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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,869	MERMELSTEIN ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *2-9 and 23-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 10-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. By Amendment filed July 07, 2006, claims 1, 11-15 and 19 have been amended and claim 18 has been cancelled. Claims 1-41 are pending in the application. However, claims 2-9 and 23-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Claims 1 and 10-22 are currently pending for prosecution on the merits of the instant application.

Summary of Action

3. The rejection of the claims 1, 10, 11 and 17 under 35 U.S.C. 102(b) as being anticipated by Unger (WO 98/51282) is not maintained in light of the amendment filed July 07, 2006.

4. The rejection of the claims 1, 10, 17, 18 and 21 under 35 U.S.C. 102(b) as being anticipated by Collier et al. (WO 00/24396) is maintained for the reasons of record.

5. The rejection of the claims 1 and 10-22 under 35 U.S.C. 103(a) as being unpatentable over GB 1330878 (Bristol Myers Co.) in view of Williams et al. (US 6638981 B2) is maintained for the reasons of record.

6. The provisional rejection of the claims 1 and 10-22 under the judicially created doctrine of double patenting over claims 1-13 and 24-25 of copending Application No.10/256283 is maintained for the reasons of record since no Terminal Disclaimer has been filed and approved yet in our PTO record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 10, 17, 18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Collier et al. (WO 00/24396).

Collier teaches a composition comprising NMDA receptor antagonist (i.e., eliprodil and ifenprodil) and preservative (i.e., benzalkonium chloride) in a suitable carrier (i.e., water and sodium chloride), wherein benzalkonium is present in said composition in the amount of 0.01% to 5% by weight, preferably 0.01% (page 2, line 20 thru page 3, line 4; Example 3 and 6)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1 and 10-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 1330878 (Bristol Myers Co.) in view of Williams et al. (US 6638981 B2).

GB'878 teaches a composition comprising ketamine and preservative such as benzethonium chloride, wherein the dosage range of ketamine is used from about 1 to 2mg/kg in intravenous administration or from about 5 to 15mg/kg in intramuscular administration (see especially page 2, lines 29-50).

Williams is being supplied as a reference to demonstrate benzalkoium chloride as functional equivalents to benzethonium chloride (column 15, lines 53-64).

The teaching differs from the claimed invention in (i) use of benzalkonium; (ii) the specific dosage amounts of ketamine, namely "from about 1mg/kg to about 15mg/kg per unit dose" (claim 12), "from about 1.0mg/kg to abut 4.5mg/kg per unit dose delivered I.V. and 6.5mg/kg to about 13mg/kg via intramuscular injection" (claim 13); "from about 0.01 mg/kg to about 1 mg/kg per unit dose" (claim 14); "from about 0.05mg/kg to about 0.7mg/kg per unit dose" (claim 15), "about 10 mg per unit 100 microliter dose" (claim 16); (iii) the specific dosage amounts of benzalkonium, namely "from about 0.001% to about 0.2% per unit dose" (claim 18),

"from about 0,07% to about 0.14% per unit dose" (claim 19), "about 0.002%" (claim 20); the specific dosage amounts of ketamine and benzalkonium, "10% ketamine hydrochloride and about 0.002% benzalkonium chloride" (claim 22)

As stated above, GB'878 meets the limitation of claim 1 except that employs benzalkonium quaternary ammonium preservative. However, because these two compounds were art-recognized equivalents at the time of the invention was made in those pharmaceutical arts, one having ordinary skill in the art would have found it obvious to substitute a benzalkonium chloride for benzethonim chloride.

Regarding optimization of known active and inactive ingredients in said composition, those of ordinary skill in the art would have been readily optimized effective dosages of ketamine and/or benzalkonium as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information provided in GB'878 where ketamine is used from about 1 to 2mg/kg in intravenous administration or from about 5 to 15mg/kg in intramuscular administration.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share

common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1 and 10-22 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-13 and 24-25 of copending Application No.10/256283. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Both the instantly claimed subject matter and the copending application are drawn to a composition comprising NMDA receptor antagonist and preservative, namely benzalkonium chloride. The scope of the present invention overlaps with the claims in copending application.

Response to Arguments

10. Applicant's arguments and Declaration filed July 07, 2006 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that none of Examples provided in the Collier teaches or suggests the presently claimed combination of an NMDA receptor antagonist with a preservative. Applicant asserts that one skilled in the art would recognize that (i) the formulation provided either in Example 3 or 6 of the Collier differs from the instant invention since it would not be used for injectable formulation and (ii) the formulation according to the Collier would not be able to achieve the anesthetic or analgesic amounts as required by the claimed invention.

This argument is not found persuasive. Unlike the applicant's argument, the Example 3 is directed the injectable formulation. Example 3 discloses a formulation containing 1.0% (w/v %) eliprodil and 0.01-5% (w/v%) of benzalkonium chloride, wherein said formulation is prepared with the addition of "water" for injection.

Regardless of the alleged ophthalmic formulation of the Collier over the instantly claimed "injectable formulation", there is no indication in the instant claims (claims 1, 10, 17, 18 and 21) that the claimed composition must be essentially in the form of injectable formulation. Rather, the composition required by the claimed invention is directed to any pharmaceutical compositions including oral, parenteral, ocular or ophthalmic, topical, transdermal, etc... Thus, the referenced formulation "metes and bounds" the instantly claimed invention.

For the sake of argument, even if the prior art formulation differs from the instant "injectable formulation", using "from about 0.001% to about 0.2%" of benzalkonium chloride to prepare various dosage forms including parenteral formulation of drug(s) including NMDA antagonist is well considered within the skill of the artisan (see for example USP 6015797, USP 6824791, 6602902, USP 6576636, USP 64410001 and USP 6124282).

With respect to the alleged "distinguishable" anesthetic or analgesic amounts as required by the claimed invention over the Collier, the examiner determines that the applicant's reliance on the probability that one skilled in the art would recognize that the dosage provided in the Collier in Example 3 or 6 would have "at best a local ocular effect" or be "indeterminable, as the solution does not stay at the ocular site, but rather washes away" is not sufficient to overcome the rejection of the record.

Unlike the applicant's argument, NMDA antagonists are known to have analgesic effects and delivery of said drugs in topical delivery including ocular or ophthalmic delivery is well known in the art (e.g.., USP 6197830, USP 6825203 and USP 6017961). In fact, many pharmaceutical actives, for example 0.4% ketorolac (under the commercial name of ACULAR) having analgesic property, can be delivered in ophthalmic solution for the reduction of ocular pain and burning/sting following corneal refractory surgery. Thus, the skilled artisan in the familiar art would have expected that the Collier's composition containing well known NMDA antagonist (i.e., eliprodil) would exhibit the analgesic effect. In absence showing clear evidence (accompanied by the clinical data) that the Collier's composition does not provide any analgesic or anesthetic effect, the examiner maintains that Collier anticipates the claimed invention.

Applicant's argument in the response takes the position that the presence of the unexpected results provided by the instant invention is sufficient to overcome prima facie obviousness over the prior art references in combination. Applicant states:

Applicants submit herewith a Declaration by Donna Madden pursuant to 37 C.F.R. § 1.132, providing evidentiary support to demonstrate that ketamine and benzethonium chloride exhibit neurotoxicity to a greater degree than a formulation of ketamine and benzalkonium chloride (*See* Madden Decl.). As such, the data clearly demonstrate how the preservatives benzethonium chloride and benzalkonium chloride are not interchangeable. (*Id.* ¶¶ 11-16). As noted by Ms. Madden, when a comparison between preservatives at the same dose, administered by the same route, was carried out to test neurotoxicity, the benzethonium chloride composition exhibited greater degenerative neuron incidence. (*Id.* ¶ 14). In fact, the data show a 2- to 4-fold increase in the incidence of neuron degeneration with benzethonium chloride as the preservative versus benzalkonium as the preservative, using the data from formulation test group 1 or the blended data from formulation test groups 1 and 2. (*Id.* ¶ 11).

Based on what is known in the art, and as compared to the data provided herein, applicants submit that the present invention has found that quaternary ammonium preservatives are not freely interchangeable in the sense that the benzethonium chloride has a greater neurotoxic effect than benzalkonium chloride. Since there is a discoverable objective unexpected difference between the types of preservatives, the claimed invention cannot be obvious over the cited art. *See Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut prima facie obviousness even though there was no evidence that the compound was effective against all bacteria); *see also In re Papesch*, 315 F.2d 381, 137 USPQ 43 (C.C.P.A. 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound).

Furthermore, these data support the principle advanced in this application, that in compositions of NMDA receptor antagonists, the choice of preservative can have a significant impact on neurotoxicity. With no teaching in the prior art to select a preservative that yields a composition with reduced neurotoxicity, there was no basis for combining references in accordance with the Examiner's suggestion, nor any reasonable expectation that the combined references would, in fact, teach the claimed invention. The Examiner's logic would lead to a combination with benzethonium chloride, which Applicants teach, and here demonstrate, results in a composition with greater neurotoxicity. Consequently, the claimed invention is not obvious. Accordingly, Applicants request the rejection be withdrawn.

This argument is not found persuasive. The specification defines the term "neurotoxicity" as "the level of neuron degeneration or necrosis, e.g., as measured by neuronal vacuolation or behavioral changes after exposure to the NMDA antagonist composition" (page 12, lines 18-20).

It appears in light of the definition that as long as no behavioral changes or neuronal vacuolations are observed in a subject, any composition containing NMDA receptor antagonist and from about 0.001% to about 0.2% of preservative "metes and bounds" the claimed invention.

The submitted test results (chart in no. 11, page 3 of the Declaration of Donna Madden under 37 CFR 1.132) shows 20% (SDNI "single degernative neuron incidence") in Ketamine bezethonium chloride compared to ND in 10% ketamine+0.002% benzalkonium formulation and 10% (SDNI) in 15% ketamine+0.002% benzalkonium formulation, respectively. The specification discloses that the treatment related neurotoxic lesions were not observed (ND) in both benzalkonium and benzethonium containing formulation except MK-801.

Based on the data, it is clear that ketamin and benzethonim chloride composition does not cause neurotoxic lesions (characteristic of clinical relevance in measuring the unwanted behavior changes of NMDA antagonist) as compared to ketamin and benzalkonium chloride composition. Since there is no clear guidance from the specification in how to extrapolate the number of neuron death or necrosis of neuron to the symptoms or arousal of behavioral changes, the examiner determines that the ketamine+benzethonim chloride without neurotoxic lesion "metes and bounds" the broadly defined instant composition without "any significant neurotoxicity".

As discussed above, the specification and Declaration fail to provide sufficient guidance in how to ascertain what levels of the reduction of neurotoxicity is considered to be "without significant neurotoxicity". Nor the specification provides, in terms of quantitative statement, that how much level of neuron degeneration or necrosis (or "Single Degenerative Neuron Incidence") corresponds to the unwanted behavior changes associated with NMDA antagonist. Thus, in absence showing the clear distinction (in terms of numerical values) between the level of

"neurotoxicity" and the level of "without neurotixicty", the examiner maintains that the prior art references combination makes obvious the instant invention.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. No Claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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